REMARKS

I. Specification amendments

The title and abstract have been amended to more clearly describe the present invention that Applicants deem is theirs. No new matter has been added. Applicants respectfully request the amendments be entered.

II. Claims status

Upon entry of this amendment, claims 47, 50, 58, 59, 61-63, and 65-69, will be pending. Claims 1-46, 48, 49, 52-57, 60, and 64, have been cancelled.

Claims 47, 50, 58, 59, and 61 have been amended. Claims 65-69 are new. Support for the amended and new claims can be found in the originally filed specification at, *e.g.*:

Amended or new claim	Support
47	page 5, lines 2-4; original claim 1
50	page 5, lines 9-15; original claims 4-7
58	page 19, lines 10-14; original claim 12
59	page 19, lines 15-21 and 26-29
61	page 19, line 17
65	page 5, lines 16-21
66	page 5, lines 9-15; page 19, lines 10-14; original claims 1-7 and 12
67	page 5, lines 16-21; page 19, lines 10-14; original claim 12
68	page 5, lines 9-15; page 19, lines 15-21 and 26-29
69	page 5, lines 16-21; page 19, lines 15-21 and 26-29

No new matter has been added. Applicants respectfully request the amendments be entered.

In this regard, amendment and cancellation of claims during pendency of the application are not to be construed as acquiescence to any of the objections and/or rejections set forth in any Office Action, and were made solely to advance prosecution and not to overcome any art of

record, whether considered alone or in combination. Applicants reserve the right to pursue any subject matter originally filed and/or subsequently cancelled or deleted in this or future continuing applications.

III. Concurrent Submissions

Concurrently submitted with this Amendment are a Declaration of Renè Holm, Ph.D., under 37 C.F.R. §1.132 ("the Holm Declaration") and an Information Disclosure Statement (IDS). With the submission of this IDS, all documents cited in the Holm Declaration are believed to be of record in the application.

IV. Response to rejections

A. Claims are definite

Claims 50-53 and 56-57 remain rejected under 35 U.S.C. 112(2) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter Applicants deem as their invention.

However, amended claim 50 now recites in relevant part:

> an alpha crystal form characterized by one or more of:
>
> a. an X-Ray powder diffractogram obtained using $CuK_{\alpha 1}$ radiation (λ=1.5406 Å) that has main peaks at the following 2θ-angles: 9.36; 10.23; 11.81; 13.45; 16.21; 16.57; 17.49; 18.89; 19.20; 19.63; 20.01; 20.30; 21.15; 21.53; 21.93; 22.34; 24.37; 25.34; 27.27; and 29.65;
> b. an X-Ray powder diffractogram as shown in Figure 1; and
> c. a Differential Scanning Calorimetry (DSC) trace that shows an endotherm with an onset temperature from 139-141 °C;

and claims 52-53 and 56-57 have been cancelled. Consequently, Applicants' invention is distinctly claimed and they respectfully request that the rejection be reversed.

B. Claims have written description support

Claim 64 has been rejected under 35 U.S.C. 112(1) for allegedly failing to have descriptive support in the specification as originally filed. The rejection is moot since claim 64 has been cancelled. Applicants therefore respectfully request that the rejection be withdrawn.

C. Claims are unobvious

Claims 47, 48, 50-54, 56-59, and 61-64 have been rejected under 35 U.S.C. 103(a) for allegedly being obvious over the Bøgesø et al., *J. Med. Chem.* 1995, 38:4380-92 ("the Bøgesø article") and EP 0 638 073 ("EP'073") in view of US Patent No. 4,443,449 ("US '449") ("the combined references") for reasons of record. Applicants traverse the rejection and respectfully request it be withdrawn.

For example, the Bøgesø article does not make obvious the crystalline hydrogen succinate salt of *trans*-4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I) of amended claim 1 for reasons of record. In fact, the position of the patent office ("the Office") that the:

> ...the thrust of the structure-activity results in Bogeso [sic] is the variation of substituents on the indan [sic] as well as piperazine ring. Thus a fair reading of the article would suggest that the salt forms are being employed as a form of delivery – i.e., more easily isolated as a crystalline form rather than the free base counterpart being obtained as residues as described in the experimental section[,]

(*see* p. 3, Jan. 22, 2009 Final Office Action ("2009 FOA")), also supports Applicants position that instant the crystalline hydrogen succinate salt of (I) is not obvious in view of the Bøgesø article. The Bøgesø article teaches that its goal was achieved – namely, obtaining compounds with the desired mixed profiles and potent activity in the form of, *e.g.*, the fumarate salts of (I) and its (1S,3R)-enantiomer and maleate salt of the racemate of (I). The Bøgesø article, however, is silent with respect to any other salt form of (I) or its racemate. In fact, it is silent with respect to any difficulties with the fumarate salt form of (I); and thus, fails to provide any reason to turn to a different salt form of (I) than the fumarate salt. The Bøgesø article, therefore, neither teaches one of ordinary skill in the art the instant crystalline hydrogen succinate salt of (I), nor suggests or motivates one to achieve it. *See also*, paragraph 23, Holm Declaration. Moreover, as set forth in the Holm Declaration, at the time of the invention, the Bøgesø article would not have provided one of ordinary skill a reasonable expectation of success if one pursued a

succinate salt of (I). Id. Accordingly, the instant crystalline hydrogen succinate salt of (I) is over the Bøgesø article.

Additionally, EP'073 and US '449 do not cure the deficiencies of the Bøgesø article alone or combined as previously presented and set forth in the Holm Declaration at paragraphs 24-25. Even though reliance on a reference is not limited to its preferred embodiments or working examples, but can rest on all that it fairly teaches, EP'073 and US '449 still do not provide sufficient suggestion or motivation to one of ordinary skill in the art to modify the fumarate salt of (I) from the Bøgesø article so as to achieve the instant crystalline hydrogen succinate salt of (I). A fair reading of each of these references is that they disclose succinic acid among a number of acid addition salts as mere possibilities ("possible salts") of different salt forms of its compounds than those disclosed. *Id.* at 25. As put forth in the Holm Declaration, each reference, therefore, fails to provide any reason to turn to a different salt form, much less a succinate form; and the combined references do not provide one of ordinary skill in the art the requisite reasonable likelihood of success and certainly not with respect to the crystalline salt of (I) of improved properties of solubility, dissolution and stability like that of the present invention. *Id.* at 25-26.

Applicants again respectfully remind the Office that in determining obviousness the use of hindsight is improper. The obviousness inquiry is not whether each element existed in the prior art, but whether the prior art made obvious *the invention as a whole*; (*see e.g., Hartness Int'l, Inc. v. Simplimatic Eng'g Co.*, 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1832 (Fed.Cir.1987)); and it is not proper to dissect claims and reconstruct them in piecemeal fashion by picking and choosing from any one prior art reference only so much as to support a given position using Applicants' specification as a blueprint to the exclusion of material necessary to fully appreciate what it fairly teaches (*see e.g., In re Kamm*, 452 F.2d 1052, 1056-57, 172 USPQ 298, 301-02 (CCPA 1972)). Clearly, the Office is using impermissible hindsight, using the instant claims as a blueprint, and then picking and choosing only so much of the claimed elements from each of the combined references, to the exclusion of what each fairly teaches, and then reconstructing them so as to find the instant crystalline hydrogen succinate salt of (I) obvious.

The Office has failed to establish a prima facie case of obviousness because one of ordinary skill in the art upon considering the combined references as a whole would find no rationale for choosing succinic acid as called for in the claimed hydrogen succinate salt of (I), nor find the required reasonable likelihood of success that the instant crystalline hydrogen succinate salt of (I) could be achieved. Accordingly, the obviousness rejection should be withdrawn.

Further, even if the Office maintains the present invention is *prima facie* obvious, Applicants maintain they have sufficiently rebutted the Office's case for reasons of record and the following reasons.

As set forth in the Holm Declaration, the behavior of a compound is a result of not only its molecular form, but also its solid form, which dictate its properties. *See* paragraph 8, Holm Declaration. The solid form of a compound can be one of two states: amorphous or crystalline *Id.* at 9. Crystalline compounds can exist in a single-component or multi-component state, where the latter comprises complex molecules like those in the pharmaceutical arts, as well as in more than one crystalline form. *Id.* at 10-11. As such, whether a compound will crystallize is not predictable. *Id.* 12. It was not predictable at the time the present invention was made (*i.e.*, August 18, 2003, its earliest effective filing date). *Id.* 13. The unpredictability of the art is such that even reportedly "major" advances in the field of crystal structure prediction in 2007 are arguably major only because of the enormous lack of predictably in the art. In fact, the purportedly major advances were not with respect to complex molecules. *Id.* Although it is known in the art that crystallizing a salt may be attempted if an ionizable group is present with an acceptable counterion and choosing a logical combination from which to start, even today one of ordinary skill in the art cannot predict whether a crystalline material will form from a particular acid and base reaction, the type of crystal that will form and the properties of the crystalline material. *Id.* at 14.

Consequently, the instant crystalline hydrogen succinate salt of (I) was unpredictable, and thus there was no reasonable expectation of success that it would be achieved, and in the two polymorphic forms of the present invention. *Id.* at 15-16.

Additionally, it was surprising and unexpected that the crystalline hydrogen succinate salt of (I) would have improved properties compared to the fumarate salt of (I). As stated in the Holm Declaration, its properties of stability and solubility that were disclosed in the instant specification and intrinsic dissolution rate were unexpected improvements over the fumarate salt of (I). *Id.* at 17-21. The lack of any degradation under all test conditions, even accelerated conditions, of the instant crystalline hydrogen succinate salt of (I) compared to the fumarate salt is a practical advantage, for example, with respect to shelf-life. *Id.* at 18. The much greater aqueous solubility (~9x) of the instant crystalline hydrogen succinate salt of (I) compared to the fumarate salt is a significant and practical advantage because of its influence on an improved therapeutic utility for (I). *Id.* at 19. The 20-fold greater intrinsic dissolution rate (IDR) of the instant crystalline hydrogen succinate salt of (I) compared to the fumarate salt is also a significant and practical advantage with respect to an improved therapeutic utility for (I) because it is suggestive of its bioavailability. *Id.* at 20-21.

These properties are surprising and unexpected because one of ordinary skill in the art could neither predict that the crystalline hydrogen succinate salt of (I) would be achieved nor what its properties would be as mentioned. *Id.* at 22. Also, these properties are surprising and unexpected because one of ordinary skill in the art would not have reasonably expected that a salt form of an acid having a similar molecular structure to the acid of prior art salt form would have more advantageous properties – i.e., it was surprising and not expected that the one double bond difference between the succinic acid and fumaric acid homologs would result in the respective salt form of (I) having significantly different solubility, IDR and stability, as mentioned. *Id.* at 23.

As explained in the Holm Declaration, the crystalline hydrogen succinate salt of (I) is not a result "a finite number of identified, predictable solutions" (*see* p. 4 of FOA). *Id.* at 28. The universe of pharmaceutically acceptable salts is a logical starting place for one of ordinary skill in the art; however, a number of other considerations must be made (*id.* at 28); and likely more so when the prior art provides no guidance with respect to what salt form of the compound will have the necessary properties or most optimal thereof. *See e.g., id.* at 16.

With respect to comparative data to the racemic free base of (I), which is nominally disclosed in the Bøgesø article (*see* Fig. 1), that the Office asserts is needed (*see* p. 7, May 13, 2008 Office Action), it is expected that the racemic free base would less optimal properties than its enantiomer as the crystalline hydrogen succinate salt of (I). *Id.* at 30. This is expected because it is well known that salt forms of free bases have more optimal properties than its salt form. *Id.* at 29. Thus, it is expected that the aqueous solubility of the racemic free base would be negligible compared to the instant succinate salt of (I), while both its stability and IDR would be less compared to the instant succinate salt of (I). *Id.* at 30. Moreover, Applicants note that with respect to the closest prior art compound, one of ordinary skill in the art would deem it to be the fumarate salt of (I) and not the racemic free base of (I) because the claimed invention is a salt form of (I) and salt forms are well known to often provide the optimal characteristics of a compound as just stated. *Id.* at 31.

As provide earlier herein, amended claim 1 now recites in relevant part: "[a] crystalline hydrogen succinate salt..." of (I). The specification provides that "hydrogen succinate" salt refers salt a 1:1 salt of (I) and succinic acid. *See* paragraph [0016] of the published application. Applicants therefore maintain that the Office's assertion that other salt ratios are covered by the claims is moot.

Clearly, as explained in the Holm Declaration, the crystalline hydrogen succinate salt of (I) is a surprising, unexpected and unpredictable success. *Id.* at 8-32.

Consequently and because of all of the reasons set out above, the present claims are not obvious over the combined references; and withdrawal of the obviousness rejection is respectfully requested.

D. IDSs – duplicate entries and Cox reference

Applicants thank the Office for indicating duplicate entries and will try to clarify the situation with respect to the Cox reference since the previous attempt was unsuccessful. Applicants have not submitted a full text copy of the Cox reference in any application since it is a 344 page text book ("Preparative Enantioselective Chromatography", Oxford, UK: Blackwell Publishing LTD. 2005) because of its voluminous nature as indicated in the 2/21/08 IDS communication. It was disclosed as such because it was cited without page citation in an

application covering similar subject matter with respect to describing that chiral chromatography can be scaled up using suitable technologies, e.g. simulated moving bed technology (SMB), or sub- or supercritical fluid technology. Accordingly, it is not being resubmitted particularly pointing out the pertinent pages. Applicants understand that the Office, thus, will not consider the reference under MPEP 609 (applicants

V. Conclusion

Because of the foregoing, the claimed invention is patentable. Early reconsideration and allowance of all pending claims is respectfully requested. Applicants respectfully request that the Office telephone the undersigned if deemed otherwise in order to facilitate allowance of the claims.

The Commissioner is hereby authorized to charge any fee or credit to Deposit Account No. 503201.

Respectfully submitted,

Lundbeck Research USA, Inc.
215 College Road
Paramus, New Jersey 07652
(201) 261-1331 Ext. 790

/Margaret M. Buck. Reg. No. 54,010/

Margaret M. Buck, Esq.
Registration No. 54,010